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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,255	08/15/2003	William P. Dole	52339AUSM1	3168

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LISA A. HAILE, Ph.D
DLA PIPER US LLP
4365 EXECUTIVE DRIVE, SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/642,255	DOLE ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 March 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *21 March 2008*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,5-11,16-26,32-36 and 38-42*.
   Claim(s) withdrawn from consideration: *31 and 37*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☒ Other: See Continuation Sheet.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: the claims stand rejected over the cited prior art. Claims 1-2, 5-7, 9-10, 16-26, 32-36 and 38-40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al, Fleming et al and Fulton et al.

Applicant argues that Fleming et al describe eNOS mutants with an Ala or an Asp substituted for the wild-type Thr at position 495 and demonstrates a difference between the two mutants in sensitivity to activation by Ca2+ and calmodulin. However, Fleming et al do not teach that these mutants have an increase in eNOS activity compared to wild type eNOS. For example, Ala or Asp substitution at residue 495 required twice the concentration of free Ca+2 and 3 times the amount of CaM to achieve the equivalent activity of wild type eNOS. This data suggests that at the same concentration of Ca+2 and CaM, the eNOS activity of the mutants would be less than wild type, given the trend of increasing activity with increasing concentration of the two agents. Such data does not support the position that Fleming et al. teach a mutant with increased eNOS activity. Further, because Fulton et al describe an eNOS with mutation at serine 1177 with an intact calmodulin-binding domain, the combination of the references would not achieve the invention as claimed; i.e., a method of treatment of CLI with a mutant comprising a substitution at residue 495 or substitutions at residues 495 and 1177, where the mutant has increased eNOS activity, as compared to wild-type eNOS polypeptide. Therefore, one of skill in the art would not be motivated to combine such teachings. Thus, because the teachings of Smith et al. would not result in the invention as claimed when combined with the teachings of Fleming et al. and Fulton et al., one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings.

Applicant's argument(s) has been fully considered, but is not persuasive. The examiner notes that the experimental conditions taught in Figure 9A are not the same as that shown in Figure 9B with respect to the Ca2+ and CaM concentrations, respectively. Figure 9B also does not compare T495A to wildtype. Thus, it is unclear how Applicant interprets that the eNOS T495A mutant would be less active than wildtype eNOS given the Ca2+ and CaM concentration trends because the activity of wildtype eNOS over the same Ca2+ and CaM concentrations is not directly compared. The substantive issue is that Fleming teaches that T495A activation is Ca2+ and CaM concentration-dependent (pg 6, col. 1, paragraph 2), as is wildtype eNOS. The association of CaM with eNOS, and thus the initiation of NO production, is regulated by the Ca2+-dependent dephosphorylation of eNOS at T495. Fleming et al discuss that those of ordinary skill in the art recognized that phosphorylation at T495 by PKC inhibits eNOS activity, that a PKC inhibitor that blocks the inhibitory phosphorylation of eNOS at T495 results in enhanced NO production (pg 7, col. 1, last paragraph). Thus, one of ordinary skill in the art would reasonably conclude that the T495A mutation obviates this regulatory dephosphorylation requirement and would result in an eNOS having increased activity as compared to wildtype eNOS.

As for why one the artisan would combine the teachings of Fleming with Fulton, Applicant appears to have overlooked Fleming's suggestion that "maximal activation of eNOS at physiological concentrations of Ca2+ and CaM requires the simultaneous phosphorylation of Ser1177 and dephosphorylation of Thr495 (pg 7, col. 2, lines 4-8). The artisan would reasonably look to combine the teachings of T495A (Fleming), that mimics the dephosphorylation of T495 with the S1177D mutation (Fulton) that results in a gain-of-function enzyme (pg 599, Figure 3 and legend). Thus, the combined teachings of Smith et al, Fleming et al and Fulton et al would result in the instantly claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the examiner has only used the teachings of the prior art, interpreted with the understanding of the ordinary artisan's knowledge and level of skill at the time of the invention.

Claims 1, 9, 35-36, 38, 40 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al, Fulton et al and Fleming et al, as applied to claims 1-2, 5-7, 9-10, 16-26, 32-36 and 38-40 above, and in further view of Alberts et al.

Applicant incorporates the argument regarding the teachings of Smith et al, Fulton et al and Fleming et al into the instant rejection.

Applicant's argument(s) has been fully considered, but is not persuasive. The examiner incorporates the teachings of Smith et al, Fulton et al and Fleming et al, and why their teachings render the instant invention prima facie obvious discussed above into the instant argument. The substantive issue of the instant rejection is the obviousness to substitute Alanine for Valine, Leucine or Isoleucine, each recognized in the art as being non-polar and uncharged amino acids. Applicant has not contested the obviousness for the ordinary artisan to make such substitutions.

Claims 1, 8-11, 35-36 and 41-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al, Fulton et al, Fleming et al and Alberts et al as applied to claims 1-2, 5-7, 9-10, 16-26, 32-36, 38-40 and 42 above, and in further view of Liu et al.

Applicant incorporates the argument regarding the teachings of Smith et al, Fulton et al and Fleming et al into the instant rejection.

Applicant's argument(s) has been fully considered, but is not persuasive. The examiner incorporates the teachings of Smith et al, Fulton et al and Fleming et al, and why their teachings render the instant invention prima facie obvious discussed above into the instant argument. The substantive issue of the instant rejection is the obviousness to combine the G2A mutation taught by Liu et al with the single or double mutant eNOS mutation(s) taught by Fulton et al and Fleming et al to produce an eNOS having increased activity as compared to wildtype eNOS. Applicant does not contest the obviousness of combining such mutations into the same eNOS polypeptide to obtain an eNOS having increased activity as compared to wildtype eNOS.

Continuation of 13. Other:

Amendments

In the reply filed March 21, 2008, Applicant has cancelled claims 3-4, 12-15 and 27-30, withdrawn claims 31 and 37, and amended claims 1, 16-18, 20, 22, 26, 32-33 and 35-36.

Priority

The examiner acknowledges the typographical error regarding the filing date of the provisional application 60/403,637. Accordingly, the effective priority date of the instant application is granted as August 16, 2002.

Drawings
The corrected drawing filed on March 21, 2008 is accepted.

Objections
The objections to claims 1 and 20 are withdrawn in light of the amendments to the claims.